STORY OF DISCOVERY

Leptin as a Treatment for Lipodystrophy: A Translational Success Story

This story begins with an obese mouse and ends with a medical treatment for people who may lack fat tissue altogether. The common link that ties together these two very different entities is a hormone called leptin. Identifying this link was a result of the collaboration among many investigators over several years, including NIDDK-supported scientists at universities, scientists in the NIDDK Intramural Research Program, industry researchers, and many others. This translational success story is a demonstration of how exciting discoveries in the laboratory are used to improve the health of people.

The Obese Mouse and the Discovery of Leptin

In 1950, scientists identified a new mouse model that was extremely obese. They called the unknown gene causing the obesity "*ob*." By the 1980s, the identity of the *ob* gene was still unknown, but it was becoming more and more apparent that research on genetic contributors to obesity was critically important to pursue. Therefore, the NIDDK sought to support research to identify obesity-related genes in rodents, including the *ob* gene. The Institute sponsored a workshop on this topic and developed an initiative to solicit research applications. In 1989, the NIDDK awarded a grant to Dr. Jeffrey Friedman through this initiative. Dr. Friedman's subsequent pioneering research led to the 1994 discovery of the mouse *ob* gene. The hormone produced by this gene was named "leptin," a term that derives from a Greek word meaning thin. Because the *ob* mutant mouse was obese, the scientists realized that the normal *ob* gene—and the hormone it encodes—must contribute to leanness.

The landmark discovery of leptin unleashed a wave of new research advances in fat biology and metabolism. Researchers found that leptin is secreted by fat cells and released in proportion to the amount of fat. These observations drastically altered the former view of normal fat tissue as simply a passive "fat storehouse." Research fueled by this 1994 discovery also led to the identification of a number of other substances that, like leptin, are secreted by fat cells and influence appetite and metabolism.

Studies demonstrated that obese animals deficient in leptin, including mice carrying the mutant form of the *ob* gene, lost weight when given the hormone. Therefore, researchers postulated that leptin treatment might also be useful for human obesity. There are, in fact, very rare instances of complete deficiency of leptin in humans that result in morbid obesity from infancy. Leptin treatment in these individuals caused substantial weight loss, providing hope for improved quality of life and longevity.

Unfortunately, in clinical studies done at that time, leptin administration was not effective in treating the vast majority of cases of human obesity, which are not due to leptin deficiency. In most cases, obesity results from a complex interaction among genetic variation (potentially involving many genes not yet identified) and the environment. Obese individuals, in fact, usually have very high levels of leptin, probably a consequence of the many fat cells secreting it. The inability of the high levels of leptin to decrease body weight suggests that the more common forms of obesity are associated with a resistance to leptin's actions. Although these results were disappointing, scientists did not give up in their quest to use this new knowledge to benefit people.

Testing Leptin as a Treatment for Lipodystrophy

Scientists in the NIDDK's Intramural Research Program had broad experience with respect to

STORY OF DISCOVERY

studying people with various forms of insulin resistance. Using this experience and knowledge, they identified a patient population—people with lipodystrophy—who could potentially benefit from leptin treatment.

Lipodystrophy is actually a group of disorders with disparate origins but with a common set of characteristics. Individuals with lipodystrophy lack fatty tissue in the face, neck, or extremities. They sometimes have central obesity and sometimes lack fat tissue altogether. While lipodystrophy is characterized by the loss of fatty tissue in certain areas of the body, tissues such as liver and muscle exhibit significant abnormal accumulation of fat, which impairs metabolic activity. These patients also exhibit resistance to the effects of insulin and are thus at high risk of developing diabetes. They may also have a range of lipid abnormalities. Treatment of lipodystrophy has included the administration of insulin, oral hypoglycemic (blood glucose lowering) agents, and lipid-lowering drugs. In spite of treatment, patients with lipodystrophy continue to have severely high levels of triglycerides, leading to recurrent attacks of acute inflammation of the pancreas; severe problems controlling blood glucose levels, posing risks of diabetic eye and kidney disease; and fat accumulation in the liver, which can result in cirrhosis and liver failure.

Because many people with lipodystrophy have low leptin levels, and because research had demonstrated beneficial effects of leptin on insulin sensitivity and fat metabolism in a number of tissues, researchers in the NIDDK Intramural Research Program and their collaborators investigated whether leptin treatment could ameliorate conditions associated with lipodystrophy. In two small clinical studies of individuals with lipodystrophy treated for short periods of time (3-8 months), leptin therapy had dramatic benefits. In one study of female patients with different forms of lipodystrophy, most of whom also had type 2 diabetes, leptin therapy improved blood glucose levels, lowered triglyceride levels, and decreased liver fat content. In another study, leptin therapy markedly improved insulin sensitivity, lowered lipid levels, and decreased liver fat content in individuals with severe lipodystrophy who also suffered from poorly controlled type 2 diabetes. Patients in these studies were able to reduce or discontinue their diabetes medications.

Seeing such dramatic results, the researchers next examined the effect of long-term leptin therapy (12 months) in patients with severe forms of lipodystrophy and poorly-controlled diabetes. Long-term leptin therapy had similarly remarkable results. Patients had improved blood glucose and blood lipid levels, and decreased fat in their livers. The patients also reported a dramatic reduction in their appetite, which led to moderate reductions in their weight. In addition, patients were able to discontinue or reduce their diabetes medications. These exciting results suggested that leptin was an effective treatment for severe lipodystrophy.

The scientists also examined the effect of leptin on other metabolic abnormalities associated with lipodystrophy. For example, female patients often have irregular or absent menstrual cycles. Leptin treatment was found to be corrective of that condition—eight of eight female patients achieved normal menstrual function following leptin therapy. In a study of 10 patients, leptin effectively improved liver function and reduced liver fat content in people with lipodystrophy and nonalcoholic steatohepatitis, a progressive metabolic liver disease. In a study of 25 patients with lipodystrophy, researchers found that a surprisingly high number had some form of kidney disease. Leptin treatment was found to improve their kidney function. Thus, leptin corrected a broad range of metabolic defects associated with lipodystrophy.

Lipodystrophy can either be inherited or acquired, and can be complete (near total lack of fat) or partial (fat loss in certain parts of the body). Clinical trials

conducted by scientists in the NIDDK Intramural Research Program and their collaborators examined leptin treatment for various forms of lipodystrophy and found that leptin effectively treated all forms tested. These results suggest that leptin is generally effective for treating lipodystrophy, independent of the underlying cause.

Testing Leptin for Treating Lipodystrophy: A Team Effort

The clinical trials testing leptin therapy for lipodystrophy conducted by the NIDDK Intramural Research Program required numerous collaborators, and spawned new collaborations. Leading this effort was Dr. Phillip Gorden, a former NIDDK Director who returned to the laboratory to continue his research. Because leptin was manufactured by industry, the Intramural Research Program and the NIDDK Office of Technology Transfer and Development worked with industry to obtain the leptin needed for the studies. In addition, because lipodystrophy affects the liver and kidneys, scientists in the Intramural Research Program with expertise studying those organs were valuable contributors to the studies. Furthermore, collaborators external to the NIDDK have studied the genetic underpinnings of different forms of inherited lipodystrophy; several genes have now been identified. Finally, many of the patients were evaluated and treated at the NIDDK's Metabolic Clinical Research Unit, a new facility in the NIH Clinical Center that enables scientists to make precise metabolic measurements. It was only through the contributions of all of these collaborators that this translational success story came to fruition.

Looking to the Future

Looking to the future, scientists are continuing research on leptin and exploring approaches for its use in treating other diseases and disorders. As described in this story, knowledge gained from studying a common condition, obesity, led to the discovery of leptin and a treatment for a very rare disease, lipodystrophy. Scientists are now coming full circle by building on the successful clinical studies with leptin in lipodystrophy and applying it to research on common diseases. For example, the NIDDK Intramural Research Program is conducting studies to examine leptin's effects on treating people with other forms of severe insulin resistance and other common metabolic conditions. If leptin proves effective in these cases, these studies would be an example of how research on rare diseases may additionally benefit people with more common diseases and syndromes. The discovery of leptin has led—and continues to lead—to a cascade of exciting and unexpected findings with broad implications for improving health.